REMARKS/ARGUMENTS

Claims 7-10 and 12 - 35 are pending.

New claim 27 is supported in the specification on page 16, line 25 and page 35, line 6.

New claims 28 - 31, correspond to claim 27, 30, 34 and 36 of co-pending application No. 09/242,977, which has been allowed to go abandoned in order to avoid a double patenting rejection.

New claims 32 to 35 are supported on page 9, lines 10-14; page 29, lines 10-15; and throughout the specification.

No new matter is added by this rejection.

I. Rule 132 Declarations

Applicants are providing herewith two Declarations pursuant to 37 CFR 1.132. In the attached Declaration by Dr. Gao, it is demonstrated that a substantial amount of contaminating adenovirus proteins or noninfectious adenovirus particles is retained in the rAAV preparation when only one or two rounds of cesium chloride gradient centrifugation are performed. This is demonstrated in an alkaline phosphatase assay performed on a rAAV preparation not subject to heat inactivation, to compare the amount of infectious adenoviral particles remaining in the preparation following one or two rounds of cesium chloride gradient centrifugation, as compared to the rAAV of the present invention.

However, as stated above, the alkaline phosphatase assay does not provide a complete picture of the amount of contaminating adenovirus retained in the preparation, as it does not measure contaminating adenoviral proteins or noninfectious adenoviral particles. In the Declaration of Dr. Gao, the data provided in the Western blots further demonstrates that the methods of Podsakoff, US 5,858,351, can not achieve the level of purity required by the present invention. This is illustrated in the figures to the Declaration, which show a clear difference in purity between those preparations purified according to Podsakoff (Spin 1) or even Spin 2, and those

purified according to one method described in the present invention (Spin 4). Thus, not only does the cited art not recognize that removal of contaminating adenoviruses is required, it does not teach methods capable of achieving the level of purity required by the present invention.

The Declaration of Dr. Wilson is provided to further scientific insight into the experimental data presented in the Declaration of Dr. Gao, and further supports the position that immunogenicity is conferred by the presence of contaminating adenovirus, regardless of whether it is infectious or non-infectious.

Dr. Wilson's Declaration also asserts that, having been taught by the present invention that removal of more contaminating adenovirus than can be achieved by the methods of Podsakoff is required to modulate the immune response to the rAAV preparation, one of skill in the art would understand that other methods could be substituted for the four rounds of cesium chloride gradient centrifugation exemplified in the present specification.

In view of the teachings of the present invention, it will be understood that it is the presence of the contaminating helper adenoviruses and adenoviral proteins in an rAAV preparation which contributes to an inflammatory response and a destructive immune response upon delivery to a subject. The cited art fails to recognize this problem or to teach a solution to this problem.

The specification teaches that the rAAV is purified to a level such that undesirable immune responses caused by adenoviral contaminants are modulated. The specification teaches that this level of purity can be achieved by appropriate purification means known to one of skill in the art.

II. 35 USC 112

Applicants note that claims 25 and 26 are free of these rejections, which are applied against the claims that recite "at least as free of contamination with a helper virus as is obtained by subjecting the rAAV to four rounds of cesium chloride gradient centrifugation".

A. Claims 7-10 and 12-24 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention.

Applicant respectfully traverses this rejection.

The relevant question is whether there is sufficient written description to inform a skilled artisan that Applicants were in possession of the claimed invention as a whole at the time the application was filed.

The specification teaches that the rAAV is purified from sufficient amounts of contamination with helper adenovirus that undesirable immune responses are avoided. The specification teaches that this level of purity can be achieved by appropriate purification means known to one of skill in the art.

Subjecting the rAAV of the invention to four rounds of cesium chloride gradient centrifugation is a means by the inventors removed adequate amounts of contaminating adenoviral helper to avoid undesirable immune responses. The specification teaches how to purify rAAV by performing four rounds of cesium chloride gradient centrifugation. The invention further describes a method of detecting the amount of contaminating adenovirus in a rAAV preparation. See, page 35, lines 1-5. Additionally, methods for detecting antibody responses and cytotoxic immune responses were known in the art as of the filing date of the application. Some of these techniques are described in the application.

Applicants submit that one of skill in the art upon reviewing the specification would have possession of the claimed invention, as of the filing date of the application. This is further supported by the statements in Dr. Wilson's Declaration, provided herewith.

Reconsideration and withdrawal of these rejections is requested.

B. Claims 7-10 and 12-24 are rejected under 35 USC 112, second paragraph, as being indefinite for the reasons of record

The examiner has maintained this rejection on the basis that the metes and bounds of the claims are not clear because, in his opinion, it is not clear what is more free than obtained by four rounds of CsCl gradient centrifugation.

Applicants traverse this rejection on the basis that the metes and bounds of the claims are clear to one of skill in the art.

One of skill in the art, having been provided with the information in the specification, one of skill in the art would have been familiar with other techniques that would achieve at least the same level of purity as provided by 4 rounds of CsCl gradient centrifugation.

Further, sensitive methods for determining level of purity including, *e.g.*, PCR, were known to those of skill in the art, would allow them to detect level of purity obtained by 4 rounds and other techniques for achieving same. Applicants are not required to teach in the description methods known to those of skill in the art. For these reasons, the present specification provides adequate description of the invention to those of skill in the art.

These facts are supported by the Rule 132 Declarations supplied herewith.

Reconsideration and withdrawal of these rejections is requested.

III. 35 USC 102 and 35 USC 103

A. Claims 7-10, 18 and 23 are rejected under 35 USC 102(e) as being anticipated by Podsakoff et al, US 5,858,351.

As demonstrated in the appendant Rule 132 Declarations, the methods described in Podsakoff are not sufficient to remove helper adenoviruses at the level recited in the claims, but only to reduce the ability of the helper adenoviruses to infect and/or express adenovirus proteins. Thus, the cited art teaches rAAV preparations with decreased adenoviral function. The cited document does not teach rAAV as free of contamination with helper adenoviruses as obtained by the present invention.

Applicants request reconsideration and withdrawal of this rejection.

B. *Claims 7-10, 18-24 and 25-26 are rejected under 35 USC 103(a) as being unpatentable over Podsakoff et al, US 5,858,351 in view of Kashyap, et al, J. Clin Invest, 96:1612-1620.*

Applicants respectfully traverse this rejection because the cited documents do not suggest rAAV as free of *contamination* with helper adenoviruses as provided by the present invention.

As demonstrated in the appendant Rule 132 Declarations, the methods described in Podsakoff are not sufficient to remove helper adenoviruses, but only to reduce their ability to infect and/or express adenovirus proteins. Further, because neither of the cited documents recognize the presence of contaminating adenoviruses (or their proteins) in their rAAV preparations, they fail to recognize the problems associated with the immunogenicity of helper adenoviruses and the ability of these helper adenoviruses to raise an inflammatory response and destructive cellular immune response in the subject. For these reasons, the cited art fails to suggest the present invention.

Reconsideration and withdrawal of this rejection is requested.

C. *Claims 7-10, 12-17, and 25-26 are rejected under 35 USC 103(a) as being unpatentable over Podsakoff et al, US 5,858,351 in view of Fang et al, Hu Gene Therapy, 6:1039-1044 (1995) and Kay et al, US 5,980,886.*

Applicants respectfully traverse this rejection because the cited documents do not suggest rAAV as free of *contamination* with helper adenoviruses as provided by the present invention.

The methods described in Podsakoff are not sufficient to remove helper adenoviruses, but only to reduce their ability to infect and/or express adenovirus proteins. Further, because the cited documents do not recognize the presence of contaminating adenoviruses (or their proteins) in their rAAV preparations, they fail to

recognize the problems associated with the immunogenicity of helper adenoviruses and the ability of these helper adenoviruses to raise an inflammatory response and destructive cellular immune response in the subject. For these reasons, the cited art fails to suggest the present invention.

Reconsideration and withdrawal of this rejection is requested.

IV. Double Patenting

A. Claims 7-10 and 12-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of US Patent No. 5,866,552.

Applicants agree to file a terminal disclaimer over the '552 patent at such time as the claims are considered to be otherwise in condition for allowance.

B. Claims 7-10 and 12-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over co-pending application number 09/242,977.

The cited application is now abandoned, rendering this rejection moot. Withdrawal of this rejection is requested.

The Director of the US Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to Deposit Account No. 08-3040.

Respectfully submitted,
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